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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,123	03/16/2001	Sharon Erickson	GENENT.073A2	6508

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EXAMINER	
SANG, HONG	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/811,123	ERICKSON ET AL.	
	Examiner	Art Unit	
	Hong Sang	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4-6,8-21,24-48 and 55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4-6,8-21,24-48 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/8/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

RE: Erickson et al.

1. Applicant's amendment filed on 9/8/2005 is acknowledged. Claims 5, 6, 14, 18 and 55 are amended.

2. Claims 2, 4-6, 8-21, 24-48 and 55 are pending and under examination.

3. The text of those sections of Title 35, U.S.Code not included in this action can be found in a prior office action.

4. It is noted that the application claims priority to U.S. Application No. 09/602,530, which is now converted to the Application No. 60/327,563. The first line of the specification should be updated accordingly.

Rejections Withdrawn

5. The rejection of Claims 14-19 under 35 U.S.C. 112, 1st paragraph as failing to comply with the written description requirement because of new matter is withdrawn in light of applicant's amendment deleting the new matter.

Response to Arguments

6. The rejection of claims 55, 2, 4, 5, 8-12, 14-17, 20, 21, 24-33, and 38-41 under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in view of Hudziak (U.S. Patent 5,725,856; issued Mar. 10, 1998; effective filing date Jan.

12, 1988) and further in view of Lewis (Lewis, G.D. et al, Cancer Immunol. Immunother. 37: 255-263, 1993; cited in the IDS) is maintained.

The response and two Declarations from Dr. Sliwkowski and Dr. Lutzker filed on 9/8/2005 have been carefully considered but are deemed not to be persuasive.

Claim 55 as currently amended requires a step of identifying said tumor as being characterized by overexpression of an ErbB2 receptor and as being a tumor that does not respond or responds poorly to treatment with an anti-ErbB2 antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cell.

The response states that when considering the invention as a whole, it is important to note whether, as here, the inventor have identified a problem that was not recognized in the prior art (see page 13, 4th paragraph). The response states that applicants have identified a group of tumors that differ from other tumors and overexpress an ErbB2 receptor but do not respond, or respond poorly, to anti-ErbB3 antibodies alone that was not recognized in the art (see page 15, 1st paragraph) and provided a solution to treat them.

This argument is unpersuasive because prior art recognizes that there are tumors overexpressing ErbB2 antibody but unresponsive to anti-ErbB2 antibody that has a growth inhibitory effect on SK-BR-3 cell (see instant specification page 4, lines 12-16). The problem that some tumors, which overexpress an ErbB2 receptor but do not respond or respond poorly to an anti ErbB2 antibody

treatment has been recognized in the art before the instant invention was made, as evidence by Lewis et al. (Cancer Immunol. Immunother 1993, 37:255-263, IDS) and the previous clinical trials (see specification page 4, lines 12-16 and Baselga et al. J. Clinical Oncology, 1996, 14(3): 737-744, IDS). Lewis et al. teach that certain tumors (MKN7, KATOIII, COLO 201 or SW1414 cell lines see page 257, right column, 2nd paragraph and Table 2), despite exhibiting over-expression of ErbB2, did not respond to the murine monoclonal antibody 4D5 by an inhibition in growth. Baselga et al. show that about 80% patients fail to respond to the treatment of HERCEPTIN, a humanized version of antibody 4D5, although most patients in the trial expressed HER2 at the 3+ level and the HERCEPTIN used in the trial inhibited breast cancer cell growth in vitro (see page 738, 2nd paragraph, lines 9-10). Although Dr. Sliwkowski states in the Declaration that "[A]s noted in the aforementioned Lewis publication, growth of the breast cancer cells lines SK-BR-3, BT474, MDA-MB-453, MDA-MB-361 is inhibited by certain HER2 antibody (see page 2, paragraph 9) and the cytostatic effects of HER2 antibodies correlated with HER2 expression level" (see page 2, paragraph 8, lines 5-8), Dr. Sliwkowski does not comment on other tumor cells (MKN7, KATOIII, COLO201 or SW1414 cell lines) wherein the cytostatic effects of HER2 antibodies do not correlate with HER2 Expression level (see Lewis et al., Cancer Immunol. Immunother 1993, 37:255-263, IDS, page 259, 2nd paragraph and Table 2). Dr. Lutzker states that the clinical experience and clinical studies now indicate the existence of at least two populations of patients whose cancers overexpress ErbB2 and progress despite HERCETTN treatment

(see page 2, paragraph 11). Dr. Lutzker further states that these clinical studies and the recent knowledge that tumors maintain high HER2 expression despite progressing on HERCETTIN provide a strong rational for developing conjugate in the indicated patient group (see page 3, paragraph 16, lines 4-7).

The response argues that the cited references fail to provide any suggestion or motivation to combine, and also the cited references fail to provide a reasonable expectation of success.

This is not found persuasive because Lewis et al. teach that certain tumors (MKN7, KATOIII, COLO 201 or SW1414 cell lines see page 257, right column, 2nd paragraph and Table 2), despite exhibiting over-expression of ErbB2, did not respond to the murine monoclonal antibody 4D5 by an inhibition in growth. Moreover, it is known in the previous trial that only 15% patients among all the participants who express high level of HER2 respond to HERCEPTIN treatment. Therefore, there is indeed a need to develop drugs that have better in vivo efficacy than HERCEPTIN alone so that the majority of patients who cannot be treated by HERCEPTIN can be treated.

Chari teaches methods of treating cancer, comprising administering to a patient in need thereof, of an effective dose of a composition comprising one or more maytansinoids linked to a monoclonal antibody or an antibody fragment (e.g. Fab, Fab', $F(ab)_2$, where the monoclonal antibody is selective for tumor cell antigens. Chari teaches linkers for making antibody conjugates. Chari teaches treating cancer such as lung, breast, colon, prostate, kidney, pancreas, ovary

and lymphatic cancer. Chari do not teach a method of treating a tumor using a an anti-ErbB2 antibody conjugated to maytansinoid, wherein said tumor as being characterized by overexpression of an ErbB2 receptor and as being a tumor that does not respond or responds poorly to treatment with an anti-ErbB2 antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cell. However, These deficiencies are made up for in the teachings of Hudziak and Lewis et al.

Hudziak teaches the use of "immunotoxins", which are anti-ErbB2 antibodies (including 4D5 and humanized antibody) that have been conjugated to cytotoxic molecules, for the purpose of delivering the cytotoxic molecule to an erbB2-expressing tumor. Hudziak teaches that the antibody may be an antibody fragment. Hudziak teaches specific linkers.

Lewis teaches that some tumor cells (MKN7, KATOIII, COLO201 or SW1414 cell lines) that overexpress ErbB2 fail to respond to murine monoclonal antibody 4D5 by exhibiting growth inhibition (see page 261, last paragraph and Table 2). Lewis suggests using engineered antibody to target the therapeutic molecules to tumor cells (see page 262, 2nd paragraph, lines 1-7).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Chari and of Hudziak to make an anti-ErbB2 antibody conjugated to maytansinoid for the purpose of treating patients having tumors that overexpress ErbB2 because it is know in the art that an antibody conjugated to a cytotoxic agent has dual benefits of both antibody and the targeted cytotoxic agent and improves drug efficacy by

using both specific delivery and selective tumor cell killing effects, also because the prior art contemplated the use of anti-ErbB2 antibodies for the purpose of making immunotoxins (Hudziak). In other words, the prior art recognized that an anti-ErbB2 antibody could be used for the purpose of delivering a cytotoxic moiety to a tumor, especially to tumors that do not respond to the ErbB2 antibody alone even though the tumor overexpresses ErbB2. In view of the teachings of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid. In view of the fact that Hudziak clearly contemplated the use of immunotoxins in methods of treatment, and in view of the fact that a maytansinoid conjugated to an anti-ErbB2 antibody falls within the scope of a immunotoxin of Hudziak, and further in view of the fact that Lewis teaches that some tumors do not respond to anti-ErbB2 antibodies, one would have been motivated to use the antibodies of Hudziak to make the maytansinoid conjugates to the claimed methods because Hudziak teaches that ErbB2 (Her-2) is amplified or overexpressed in many human malignancies (column 2, lines 38-64) and because Lewis teaches that not all ErbB2 overexpressing tumors respond to anti-ErbB2 antibodies. One of skill in the art would have a reasonable expectation of success of making an anti-ErbB2 antibody conjugated to maytansinoid to treat tumors, which overexpress ErbB2 and do not respond or respond poorly to anti-BrbB2 antibody because prior art teaches how to make a conjugate of anti-ErbB2 antibody and cytotoxic agent and

a conjugate of monoclonal antibody and maytansinoid, moreover how to use these conjugated to treat cancers.

The applicant's response states that Lewis teaches away from the methods of the present invention.

In response to this argument, Lewis teaches that humanization of murine monoclonal antibodies allows for the large-scale production of antigen-specific targeting molecules that can be designed to deliver therapeutic agents with the specificity of the parent molecule (see page 262, 2nd paragraph, lines 1-7). Therefore, Lewis does not teach away from the method of the present invention instead Lewis suggest to use engineered antibody to target the therapeutic molecules to tumor cells. In other words, the prior art recognized that an anti-ErbB2 antibody could be used for the purpose of delivering a cytotoxic moiety to a tumor, especially to tumors that do not respond to the ErbB2 antibody alone even though the tumor overexpresses ErbB2. Thus one of skill in the art would be motivated to make antibody of ErbB2 conjugated to maytansinoid to treat tumors, which overexpress ErbB2 receptor and do not respond or respond poorly to treatment with ani-ErbB2 antibody.

The response further states that the cited references fail to provide all elements of the claimed invention.

In response to these arguments, the rejection is based on a combination of references and as such each reference does not have to teach all limitations.

7. The rejection of claims 55, 2, 4, 5, 8-21, 24-33, 38-41 and 46-48 under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in view of Carter (U.S. Patent 6,054,297; issued Apr. 25, 2000; effective filing date Aug. 21, 1992) and further in view of Lewis (Lewis, G.D. et al, Cancer Immunol. Immunother. 37: 255-263, 1993; cited in the IDS) is maintained.

The response and two Declarations from Dr. Sliwkowski and Dr. Lutzker filed on 9/8/2005 have been carefully considered but are deemed not to be persuasive. The Declarations are not persuasive for the reasons given above.

The response to the argument that the cited references fail to provide any suggestion or motivation to combine, and also the cited references fail to provide a reasonable expectation of success is set forth above (see paragraph 5).

The response to the argument that Lewis reference teaches away from the method of current invention is set forth above (see paragraph 5).

The response further states that Hudziak, Lewis, and Carter all lacks disclosure of maytansinoids, antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible use (see page 41, 4th paragraph).

The response to these arguments is the rejection is based on a combination of references and as such each reference does not have to teach all limitations. The teaching for treating ErbB2 overexpressing tumors is shown by

Lewis et al. who suggest using engineered antibody to target therapeutic molecules to tumor cells. Carter teaches humanized 4D5 antibodies and teaches each of the species of named species (huMab4D5-1, huMab4D5-2, huMab4D5-3, huMab4D5-3, huMab4D5-4, huMab4D5-5, huMab4D5-6, huMab4D5-7, and huMab4D5-8) by the disclosure of how to make these antibodies. Carter also teaches the humanized 4D5 antibodies may be used as immunotoxins, where they are conjugated with a cytotoxic moiety.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Chari and of Carter to make an immunotoxin, particularly a humanized anti-ErbB2 antibody conjugated to maytansinoid for the purpose of treating patients having tumors that overexpress ErbB2 but do not respond or respond poorly to the treatment of anti-ErbB2 antibody. In view of the fact that Carter clearly contemplated the use of immunotoxins in methods of treatment, and in view of the fact that a maytansinoid conjugated to an anti-ErbB2 antibody falls within the scope of a immunotoxin of Carter, and further in view of the fact that Lewis teaches that some tumors do not respond to anti-ErbB2 antibodies, one would have been motivated to use the antibodies of Carter to make the maytansinoid conjugates to the claimed methods because Carter teaches that ErbB2 (Her-2) is amplified or overexpressed in many human malignancies and because Lewis teaches that not all ErbB2 overexpressing tumors respond to anti-ErbB2 antibodies.

8. The rejection of claims 55, 2, 4-6, 8-12, 14, 20, 24-33 and 38-41 under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in view of Bacus (U.S. Patent 5,514,554; issued May 7, 1996; filing date Oct. 7, 1993) and further in view of Lewis (Lewis, G.D. et al, Cancer Immunol. Immunother. 37: 255-263, 1993; cited in the IDS) is maintained.

The response and two Declarations from Dr. Sliwkowski and Dr. Lutzker filed on 9/8/2005 have been carefully considered but are deemed not to be persuasive. The Declarations are not persuasive for the reasons given above.

The response to the argument that the cited references fail to provide any suggestion or motivation to combine, and also the cited references fail to provide a reasonable expectation of success is set forth above (see paragraph 5).

The response to the argument that Lewis reference teaches away from the method of current invention is set forth above (see paragraph 5).

The response further states that "Neither Chari nor Lewis suggest any methods for treating ErbB2 overexpressing tumors that do not respond, or respond poorly to, anti-ErbB2 antibodies, and provide basis for suggesting a possible treatment and Bacus also fails to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB3 antibody" (see page 24, 3rd paragraph).

The response to these arguments is that the rejection is based on a combination of references and as such each reference does not have to teach all

limitations. The teaching for treating ErbB2 overexpressing tumors is shown by Lewis et al. who suggest using engineered antibody to target therapeutic molecules to tumor cells. Bacus teaches anti-ErbB2 antibodies that are growth inhibitory, that induce cell death and that induce apoptosis and teaches that such antibodies may be conjugated to cytotoxic moieties. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Chari and of Bacus to make an anti-anti-ErbB2 antibody of Bacus conjugated to a toxin, particularly maytansinoid for the purpose of treating patients having tumors that overexpress ErbB2. In view of the fact that Bacus clearly contemplated the use of immunotoxins in methods of treatment, and in view of the fact that a maytansinoid conjugated to an anti-ErbB2 antibody falls within the scope of an immunotoxin of Bacus, and further in view of the fact that Lewis teaches that some tumors do not respond to anti-ErbB2 antibodies, one would have been motivated to use the antibodies of Bacus to make the maytansinoid conjugates to the claimed methods because Bacus teaches that ErbB2 (Her-2) is amplified or overexpressed in many human malignancies and because Lewis teaches that not all ErbB2 overexpressing tumors respond to anti-ErbB2 antibodies.

9. The rejection of claims 55, 2, 8-14, and 20, 24-33 under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in view of Huston (U.S. Patent 5,877,305; issued Mar. 2, 1999; effective filing date Feb. 6, 1992) and further in view of

Lewis (Lewis, G.D. et al, Cancer Immunol. Immunother. 37: 255-263, 1993; cited in the IDS) is maintained.

The response and two Declarations from Dr. Sliwkowski and Dr. Lutzker filed on 9/8/2005 have been carefully considered but are deemed not to be persuasive. The Declarations are not persuasive for the reasons given above.

The response to the argument that the cited references fail to provide any suggestion or motivation to combine, and also the cited references fail to provide a reasonable expectation of success is set forth above (see paragraph 5).

The response to the argument that Lewis reference teaches away from the method of current invention is set forth above (see paragraph 5).

The response further states that "Neither Chari nor Lewis teaches conjugates comprising an anti-ErbB2 antibody (or antibody fragments) and neither Chari nor Lewis teach method for treatment of metastatic breast cancer" (see page 25, 2nd paragraph). The response furthers states that Huston fails to teach maytansinoid and maytansinoid-antiErbB2 antibody conjugates.

The response to these arguments is the rejection is based on a combination of references and as such each reference does not have to teach all limitations. Huston teaches single-chain Fv comprising a binding site that binds to ErbB2 and methods of treatment of cancer comprising linking the single-chain Fv to a therapeutic agent, which is an agent that has the ability to limit the proliferation of a tumor cell. Huston also teaches methods for treatment of metastatic breast cancer. Thus, it would have been prima facie obvious to one of

ordinary skill in the art at the time the invention was made to have used the teachings of Chari and of Huston to make an immunotoxin, particularly single-chain Fv conjugated to maytansinoid for the purpose of treating patients having tumors, particularly metastatic breast cancers that overexpress ErbB2 but do not respond or respond poorly to anti-ErbB2 antibody treatment. In view of the fact that Huston clearly contemplated the use of single-chain Fv linked to a therapeutic agent in methods of treatment, and in view of the fact that a maytansinoid conjugated to an anti-ErbB2 antibody falls within the scope of a single-chain Fv linked to a therapeutic agent, and further in view of the fact that Lewis teaches that some tumors do not respond to anti-ErbB2 antibodies, one would have been motivated to use the antibodies of Huston to make the maytansinoid conjugates to the claimed methods because Huston teaches that ErbB2 (Her-2) is a tumor antigen and because Lewis teaches that not all ErbB2 overexpressing tumors respond to anti-ErbB2 antibodies.

10. The rejection of claims 55, 2, 8-12, 24-33 and 38-41 under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in view of King (U.S. Patent 5,747,261; issued May. 5, 1998; effective filing date Mar. 5, 1986) and further in view of Lewis (Lewis, G.D. et al, Cancer Immunol. Immunother. 37: 255-263, 1993; cited in the IDS) is maintained.

The response and two Declarations from Dr. Sliwkowski and Dr. Lutzker filed on 9/8/2005 have been carefully considered but are deemed not to be persuasive. The Declarations are not persuasive for the reasons given above.

The response to the argument that the cited references fail to provide any suggestion or motivation to combine, and also the cited references fail to provide a reasonable expectation of success is set forth above (see paragraph 5).

The response to the argument that Lewis reference teaches away from the method of current invention is set forth above (see paragraph 5).

The response further states that "King fails to disclose or to suggest any methods for treating a tumor in a mammal that overexpresses ErbB2a and that also does not respond, or respond poorly, to a treatment with an anti-ErbB2 antibodies" (see page 25, last paragraph). The response to these arguments is the rejection is based on a combination of references and as such each reference does not have to teach all limitations. The teaching for treating ErbB2 overexpressing tumors is shown by Lewis et al. who suggest using engineered antibody to target therapeutic molecules to tumor cells. King teaches methods for treating cancer that express high levels of ErbB2 (mac117) comprising the administration of antibodies that bind the ErbB2, where the antibody is linked to one or more agents that will cause injury to cells for the purpose of directing the toxic agent to the cancer cells that over express ErbB2. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Chari and of King to make an

immunotoxin, particularly an anti-ErbB2 antibody conjugated to more than one maytansinoids for the purpose of treating patients having tumors that overexpress ErbB2 but do not respond or respond poorly to anti-ErbB2 antibody treatment. In view of the fact that King clearly contemplated the use of an antibody linked to one or more agents that will cause injury to cells in methods of treatment, and in view of the fact that a maytansinoid conjugated to an anti-ErbB2 antibody falls within the scope of an antibody linked to one or more agents that will cause injury to cells, and further in view of the fact that Lewis teaches that some tumors do not respond to anti-ErbB2 antibodies, one would have been motivated to use the antibodies of King to make the maytansinoid conjugates to the claimed methods because King teaches that ErbB2 (Her-2) is a tumor antigen that is overexpressed in some tumors and because Lewis teaches that not all ErbB2 overexpressing tumors respond to anti-ErbB2 antibodies.

11. The rejection of claims 55, 34, 44 and 45 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (supra) in combination with Hudziak (supra), Baccus (supra), Huston (supra) or King (supra) in view of Lewis (supra) as applied to claim 55 above, and further in view of Senger (U.S. Patent 6,022,541; issued 2/8/2000; effective filing 3/3/1997) is maintained.

The response and two Declarations from Dr. Sliwkowski and Dr. Lutzker filed on 9/8/2005 have been carefully considered but are deemed not to be persuasive. The Declarations are not persuasive for the reasons given above

The response to the argument that the cited references fail to provide any suggestion or motivation to combine, and also the cited references fail to provide a reasonable expectation of success is set forth above (see paragraph 5).

The response to the argument that Lewis reference teaches away from the method of current invention is set forth above (see paragraph 5).

The response further states that Chari and Senger lack any disclosure or suggestion of anti-ErbB2 antibodies (see page 44, 2nd paragraph).

The response to the argument is that the rejection is based on a combination of references and as such each reference does not have to teach all limitations. Senger teaches an improvement of immunological methods for tumor targeting, comprising the use of at least two antibodies where each of the antibodies that binds to vascular permeability factor (VPF; which binds to tumor endothelial cells) is conjugated to an effector moiety, which may be toxin, and which may be the same or different for each of the two antibodies. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the claimed inventions comprising the administration of combinations of antibodies, where the combination of Chari with either of Baccus, Huston or King and in view of Lewis suggests a method for the treatment of cancer overexpressing ErbB2, comprising the administration of a combination of antibodies that are maytansinoid-ErbB2 conjugates to tumors that do not respond to an ant-ErbB2 antibody alone, because Senger provides an

example of a treatment strategy where an antigen is targeted with two different antibodies, where each are conjugated to a toxin.

12. The rejection of claims 55, 34-37, 42 and 43 under 35 U.S.C. 103(a) as being unpatentable over Chari (supra) in combination with Hudziak (supra), Baccus (supra), Huston (supra) or King (supra), in view of Lewis (supra) as applied to claim 55 above, and further in view of Sliwkowski (Sliwkowski, M.X. et al., J. Biol.Chem. 269: 14661-14665, 1994; IDS) or Carter (supra) is maintained.

The response and two Declarations from Dr. Sliwkowski and Dr. Lutzker filed on 9/8/2005 have been carefully considered but are deemed not to be persuasive. The Declarations are not persuasive for the reasons given above

The response to the argument that the cited references fail to provide any suggestion or motivation to combine, and also the cited references fail to provide a reasonable expectation of success is set forth above (see paragraph 5).

The response to the argument that Lewis reference teaches away from the method of current invention is set forth above (see paragraph 5).

The response further states that the claims are not obvious over the cited reference (see page 34, line 12). This is not found persuasive. Sliwkowski teaches that 2C4 may be used to inhibit the binding of heregulin (a growth factor) to ErbB3 and Carter teaches that huMab4D5-8 acts to recruit immune effector cells to a tumor. Thus, it would have been prima facie obvious to one of ordinary

skill in the art at the time the invention was made to have used a second antibody for the purposes of blocking the effects of a growth factor such as heregulin, or for the purposes of recruiting immune effector cells to a tumor.

13. The rejection of claims 55, 4-6, 8-19, 24, 25, 27 and 32 under 35 U.S.C. 103(a) as being unpatentable over Iwassa (U.S. Patent 5,217,713; issued Jun. 8, 1993; effective filing date Dec. 27, 1989) in combination with Carter (supra), Hudziak (supra), Baccus (supra), Huston (supra) or King (supra), in view of Lewis (supra) is maintained.

The response and two Declarations from Dr. Sliwkowski and Dr. Lutzker filed on 9/8/2005 have been carefully considered but are deemed not to be persuasive. The Declarations are not persuasive for the reasons given above.

The response to the argument that the cited references fail to provide any suggestion or motivation to combine, and also the cited references fail to provide a reasonable expectation of success is set forth above (see paragraph 5).

The response to the argument that Lewis reference teaches away from the method of current invention is set forth above (see paragraph 5).

The response further states that the cited references provide no suggestion or motivation. This is not found persuasive. The motivation to combine the teachings of the references is derived from the teachings of Iwassa that maytansinoids may be targeted to a tumor using a bispecific antibody that

contains one binding site that binds to a maytansinoid and a second site that binds to a tumor antigen. Each of Carter, Huziak, Baccus, Huston, or King teaches antibodies that bind to a tumor antigen, ErbB2, and teaches that these antibodies are useful in methods of targeting toxins to tumor cells. Because each of Carter, Huziak, Baccus, Huston, or King teaches the use of their anti-ErbB2 antibodies as antibodies that would act as carriers to selectively deliver a toxin to tumor cells, the motivation to combine the references is that Iwassa teaches the desirability of increasing the selectivity of maytansinoid constructs and any of Carter, Huziak, Baccus, Huston, or King teaches that anti-ErbB2 antibodies are useful as carriers to increase the selectivity of toxins.

14. The rejection of claims 55, 2, 4, 5, 8-12, 14-17, 20, 21, 24-33, and 38-41 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-18 of U.S. Patent No. 5,208,020 in view of in view of Hudziak (U.S. Patent 5,725,856; issued Mar. 10, 1998; effective filing date Jan. 12, 1988) and further in view of Lewis (Lewis, G.D. et al, Cancer Immunol. Immunother. 37: 255-263, 1993; cited in the IDS) is maintained.

The response and two Declarations from Dr. Sliwkowski and Dr. Lutzker filed on 9/8/2005 have been carefully considered but are deemed not to be persuasive. The Declarations are not persuasive for the reasons given above.

The response states that the US patent NO. 5,208,020 to Chari is not assigned to Genetech. In response to this argument, the MPEP states that a

rejection under double patenting is made if a patent application has at least one common inventor (in the instant case, the inventor Walter Blattler is the common inventor) with the issued US patent (see MPEP §804).

Conclusion

15. No claims are allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hong Sang
Art Unit: 1643
Oct. 15, 2005

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER